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## Early development of the human mesonephros

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**Abstract** The mesonephrogenic cord disintegrates into approximately 35–40 provesicular cell masses which are in close contact with the mesonephric (Wolffian) duct (WD) on their lateral side. Here, the epithelium of the WD is columnar and shares a common basal lamina with the provesicular cell masses. This in turn gives rise to a sickle-shaped pseudostratified epithelium. The concavity of the sickle is filled by spherical cells, the transition of which into the surrounding connective tissue is continuous. The sickle is transformed into a distillation flask and becomes separated from the mesonephric duct while the spherical cells maintain a connection to it by a—for the time being—solid outlet pipe. The columnar epithelium of the mesonephric duct becomes a multilayered cone, whose surface is in contact with the outlet tube. Shortly after, a continuous lumen is formed in the cone and the outlet pipe which is delimited by cells becoming columnar and forming a basal lamina. The epithelial anlage of the nephron is clearly separated from the surrounding mesenchyma by these processes. The flask eventually becomes a corpusculum, the outlet pipe a secretory (proximal) as well as collecting tubule, and the cone of the mesonephric duct a mesoureter. The various sections display differentially differentiated epithelia that are clearly distinct from each other. The mesoureter behaves differently during differentiation of epi- and paragenitale: in the epigenitale, it is short and runs into the collecting tubules of the nephrons at the lateral side of the convoluted tubules, whereas a long mesoureter crosses the dorsal side of the convoluted tubules and joins the corresponding collecting tubules at the far end of the mesonephros in the paragenitale.

**Keywords** Nephron · Mesonephros · Mesoureter · Wolffian duct · Embryology

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### Introduction

The development of the nephron in the mesonephros is reported in textbooks of embryology (Fischel 1929; Hamilton et al. 1972; Starck 1975; Moore 1980; O’Rahilly and Müller 1996) according to the mode outlined by Felix (1911): the mesonephric cord generates provesicular cell masses that become vesicles. Cells growing from the vesicles fuse with the mesonephric (Wolffian) duct (WD) and, after acquisition of a lumen, become tubules whereas the vesicle becomes the corpuscle of the nephron.

Felix (1911) does not report details on the development of the nephron, nor does he provide illustrations. He just states that “the anlagen appear suddenly” (p. 779). In a schematic graph (Fig. 561) he compiles the steps leading from a vesicle to a nephron. His view is based on his knowledge of comparative embryology, and on his belief in the “biogenetic basic law” (Haeckel 1903), even in modified form. He, therefore, claims (Felix 1911) to have identified ureters of the mesonephros (or better mesoureters) which sprout from the WD and collect caudal tubules of the mesonephros.

Since Felix (1911), nobody has cared to reexamine the early development of the mesonephros. Therefore, we took another look into the nephrons of the mesonephros in order to investigate the presence of mesoureters.

### Materials and methods

Our examination is based on all serial sections of human embryos and early fetal stages of the collection of the Department of Anatomy, University of Basel. Stages 15 through 23 and the early fetal stages are listed in Ludwig (1993). The additional embryos used in this study comprising stages 11 through 14 as well as some older stages useful for this examination are listed in Table 1.

Digital micrographs of sections from embryo 10.12.1952 (29 mm CRL) were used for reconstruction.

Using the AutoAligner module of the Imaris software package (Bitplane AG, Zurich, Switzerland), images were aligned with the ureter of the metanephros as a landmark, and truncated along the epithelial surface yielding reconstructions of the luminal space. After processing with a Gaussian filter in order to soften singular section-induced irregularities, each corpuscle and its associated tubule were reconstructed separately by surface rendering in the IsoSurface module of Imaris. Finally, the color-coded reconstructions were joined into a singular data set.

## Results

In a stage 12 embryo (appr. 3–5 mm CRL), we found 31 anlagen of developing nephrons. While the cranial nephrons are already in the vesicle stage, the mesonephric cord persists in the caudal region. Stage 13 embryos (appr. 4–6 mm CRL) show several nephrons in an early developmental stage in the caudal part of the mesonephros. A caudal provesicular cell mass that has been generated from the mesonephric cord consists of densely and irregularly packed small cells without a lumen (Fig. 1a). Dorsally it cannot be separated from the adjacent dorsal tissue but it makes contact with the mesonephric duct (Wolffian duct = WD) on its lateral side (Fig. 1a). The semicircular lumen of the WD faces the lateral side with its convex half. While the cells of its lateral wall are cuboidal, those of the medial wall form a columnar palisade (Fig. 1a) that is separated from the adjacent mesonephrogenic tissue by a basal lamina.

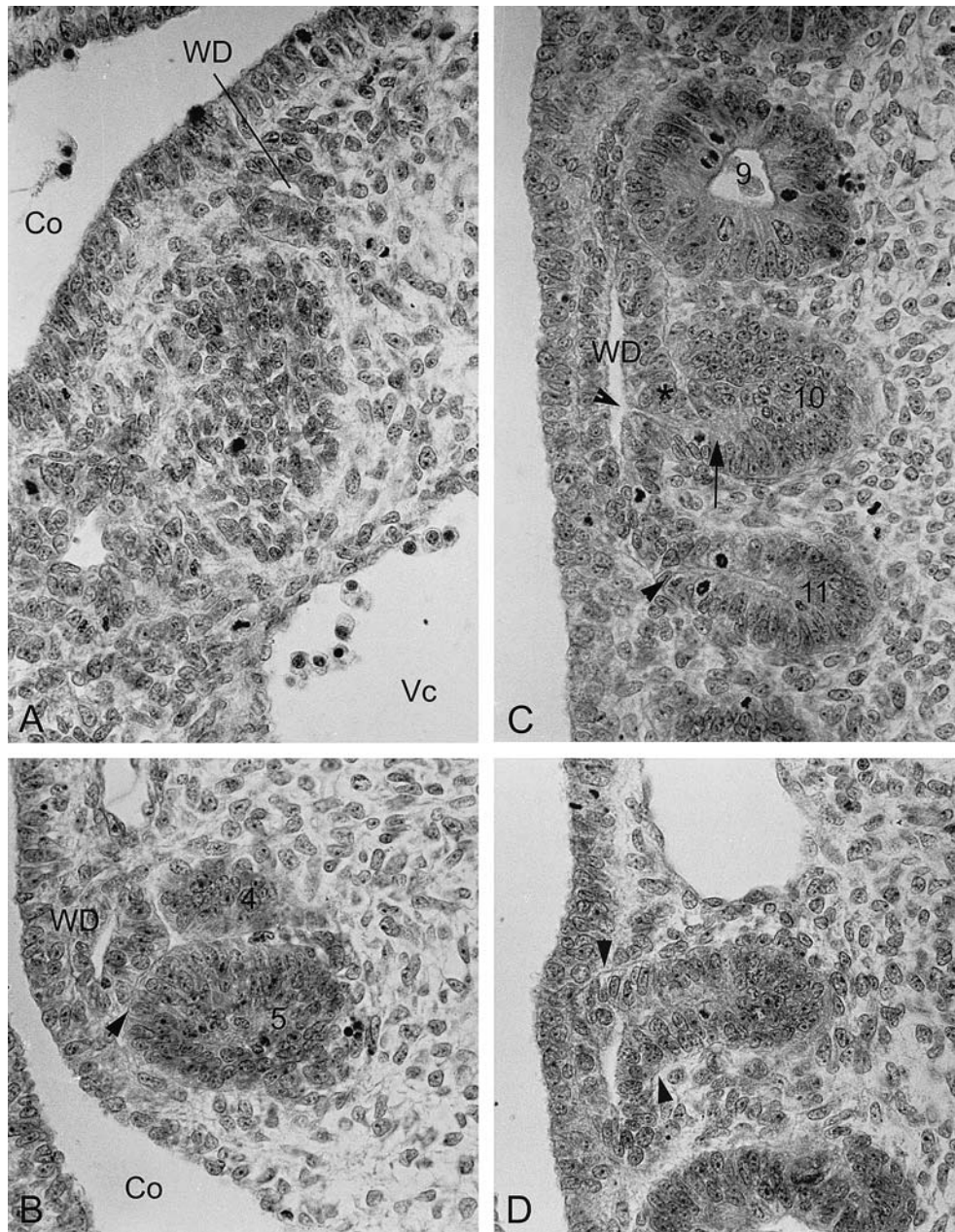
The lumen of the WD is round or oval in the intervals between the provesicular cell masses and consists entirely of cuboidal cells. With proliferation of the mesonephrogenic tissue, the cells adjacent to the WD become columnar and interact with a basal lamina, which is common for both structures in the area of contact (Fig. 1b). On the dorsal side, the cells that eventually

**Fig. 1** Embryo 28.7.59, 4.5 mm CRL (stage 13),  $\times 360$ . **a** Section of the most caudal provesicular cell mass of the mesonephros generated by the nephrogenic cord. Close to the Wolffian (mesonephric) duct (WD) the cells are densely packed; at the dorsal side the texture is less dense and forms a continuous transition into the surrounding connective tissue. The WD forms a palisade consisting of columnar cells with a basal lamina at the side of the mesonephrogenic cell mass. The palisade forms the boundary of the straight section of the semicircular lumen, whereas the curved section consists of a non-stratified, cuboidal epithelium. Co coelom, Vc cardinal vein. **b** This section shows the 4th and 5th provesicular cell masses counted from the caudal side. The 5th mass consists of densely packed columnar cells on the side of the WD while cells on the dorsal side are rather spherical. Here too, no sharp boundary against the mesenchyma is present. The palisade of the WD has become a cone sharing a common basal lamina with the adjacent provesicular cell mass (*arrowhead*). **c** Section displaying the prospective nephrons 9, 10 and 11 (counted from caudal). The 9th anlage shows the so-called vesicular stage with the flask of the distillery apparatus. Its lumen is delimited by a pseudostratified columnar epithelium. As demonstrated by the 10th anlage, the flask continues into the outlet tube consisting of densely packed cells and apposed to the conus of the WD. Right in the center of the cone, a canaliculus has been formed in situ (*arrowhead*) which extends in the draining tube. A short stalk generated by the conus of the mesonephric duct (*asterisk*) supports the draining tube (*arrow*). The 11th nephron shows that the cells become columnar and are arranged concentrically around the canaliculus. There is still no distinct boundary between nephrons and connective tissue. *Arrowhead* points to the transition between mesoureter and draining tubule. **d** The 13th prospective nephron and the mesoureter display a distinct basal lamina (*arrowhead*) separating epithelial components from connective tissue

become the nephron are small, circular and arranged irregularly. They cannot be separated unambiguously from the dorsally adjacent tissue. A small, rapidly expanding lumen becomes visible in the region of the columnar cells (Fig. 1c). This makes the anlage similar to a distillation flask: the flask which is reflected by a vesicle in cross sections (Fig. 1c, 9) is formed by columnar cells that are arranged concentrically around the lumen form. The dorsally apposed round cells form the outlet pipe which bends strongly to the dorsolateral

**Table 1** Embryos used in this study listed by stage of development (according to O’Rahilly et al. 1981)

Stage	Designation of embryo	CRL (mm)	Sex	Direction of sectioning	Thickness of sectioning ( $\mu\text{m}$ )	Stain	Notes
11	NN	3–4		Transversal	10	Coch.-Alaun	
12	Br. 1934	3.6		Frontal	8	Coch.-Alaun	
13	Embryo 28.7.54 A	4–5		Transversal	6	Azan	Twins
	Embryo 28.7.54 A	4–5		Transversal	6	Azan	Twins
	Egli 4.1.50	5–6		Transversal	6	Azan	
14	Pfy. 1	7		Sagittal	10	Coch.-Alaun	
	Ve 1	7		Sagittal	10	Azan	
	F.Sp. 43	7		Transversal	6	Azan	
15	Embryo 17.5.1951	8		Frontal	6	Azan	
16	Egli 13.1.1951	9		Transversal	6	Azan	
18	MJSp. 8.11.1940	15	f	Transversal	6	Azan	
20	Sellheim 17.1.1945	20	m	Transversal	8	Azan	
	MJSp. 17.11.1948	20	f	Frontal	6	Azan	
23	Embryo 10.12.1952	29	m	Transversal	7	Azan	
	Embryo Mensch	30	f	Transversal	7	Azan	
Early fetal stages	Riehn 1948	40	f	Transversal	8	Azan	
	Embryo 22.10.1952	40	m	Transversal	8	Azan	



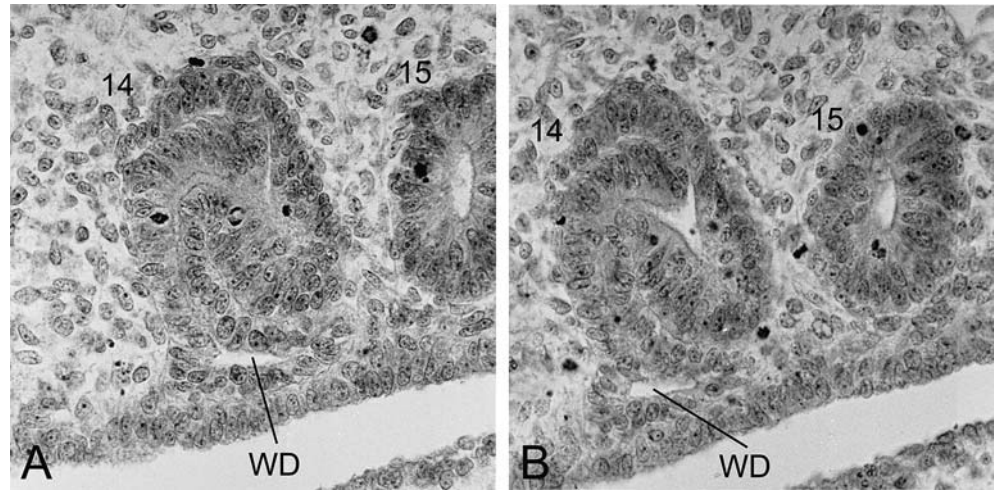
side and joins the WD (Fig. 1c, 10, cf Fig. 2). In this stage, the flask is separated from the WD by connective tissue. The palisade of the WD gives rise to an elongated, stratified slab of epithelium that—with a conical protrusion—is positioned at the outlet tube of the nephron anlage, and eventually fuses with it (Fig. 1c). Within the conical protrusion, a canaliculus is formed which leads into the nephron anlage (Fig. 1c, d). The diameter of its lumen varies between 2 and 5  $\mu\text{m}$ . It runs in the region of the columnar cells as far as the lumen of the flask (Fig. 2). The spherical cells of the anlage of the outlet tube become cuboidal or elongated, and are arranged radially around the canaliculus. At the same time, a basal lamina is formed against the surrounding tissue (Figs. 1c, 2). The vesicular lumen of the flask be-

comes flattened in the ventrodorsal axis and forms a sickle-shaped protrusion. This is the first indication of the cavity of the later corpusculum (Fig. 2).

The formation of new nephrons is terminated by stage 14 (5–7 mm CRL) with 35–38 nephrons (Fig. 3). The most caudal thickening of the WD gives rise to the ureter-bud for the metanephros (Fig. 3). In the nephron anlage the cells are arranged around the canaliculus to a pseudostratified epithelium. A basal lamina which is formed between the basis of the cells and the surrounding connective tissue constitutes a boundary of the anlage (Fig. 2). Cell proliferation and organization result in elongated canaliculi with a simple epithelium. They form loops which give rise to the typical S-shaped structure of the tubular system. Concomitantly, the

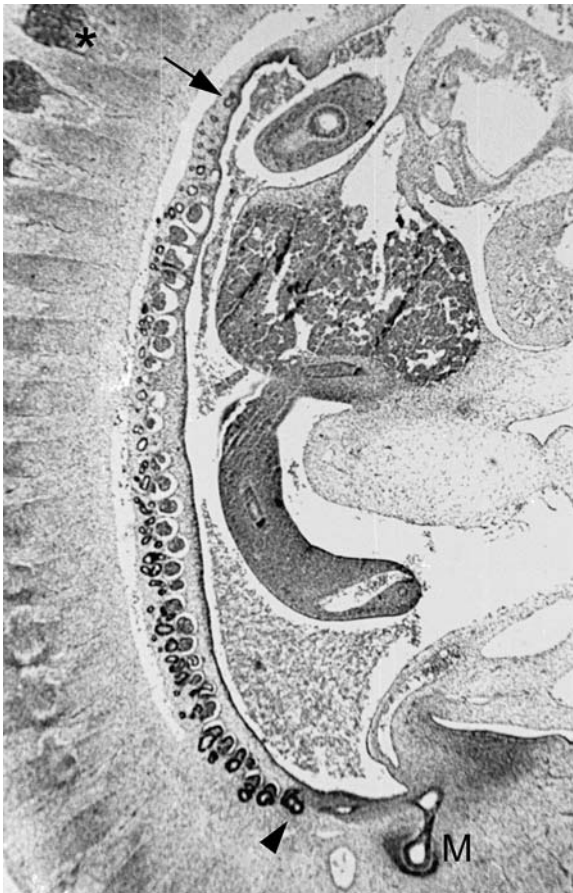


**Fig. 2** Embryo 28.7.59, 4.5 mm CRL (stage 13),  $\times 360$ . **a** and **b** show two consecutive sections of the 14th and 15th prospective nephrons. The 15th anlage demonstrates the characteristic shape of the distillery flask. The canaliculus has joined the lumen of the flask which has become flattened in ventro-dorsal direction as shown by the 14th anlage. There is a distinct boundary against the surrounding connective tissue by now. *WD* mesonephric duct

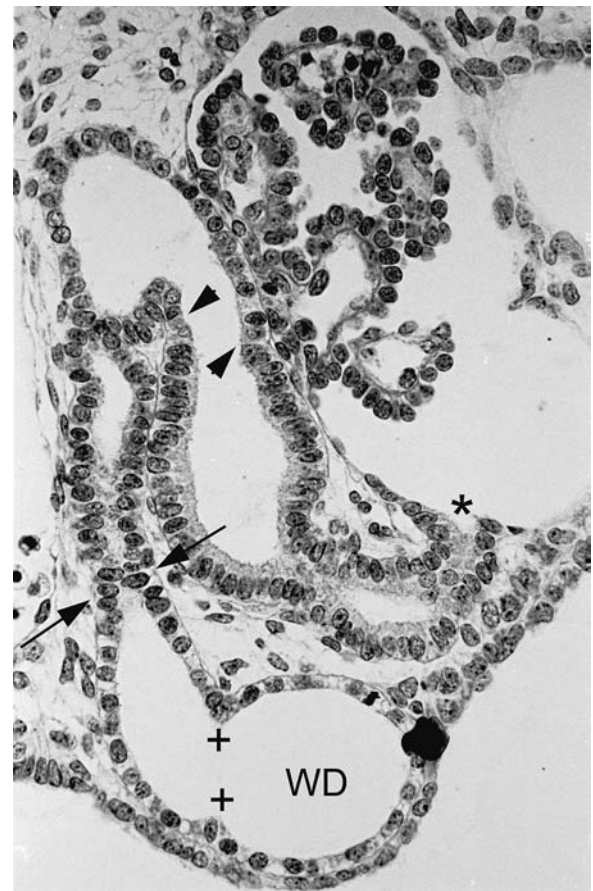


epithelia differentiate the cell types typical for the various sections of the tubules.

Stage 15 (7–9 mm CRL) is characterized by fully differentiated nephrons (Fig. 4). The corpusculum with glomerulus and Bowman's capsule gives rise at its urinary pole to the secretory (proximal) tubule, which



**Fig. 3** Embryo Pf.1, 7 mm CRL (stage 14),  $\times 36$ . This embryo shows 38 nephrons. *Arrow* 1st nephron, *arrowhead* 38th nephron, *M* anlage of the metanephros, *asterisk* spinal ganglion C6



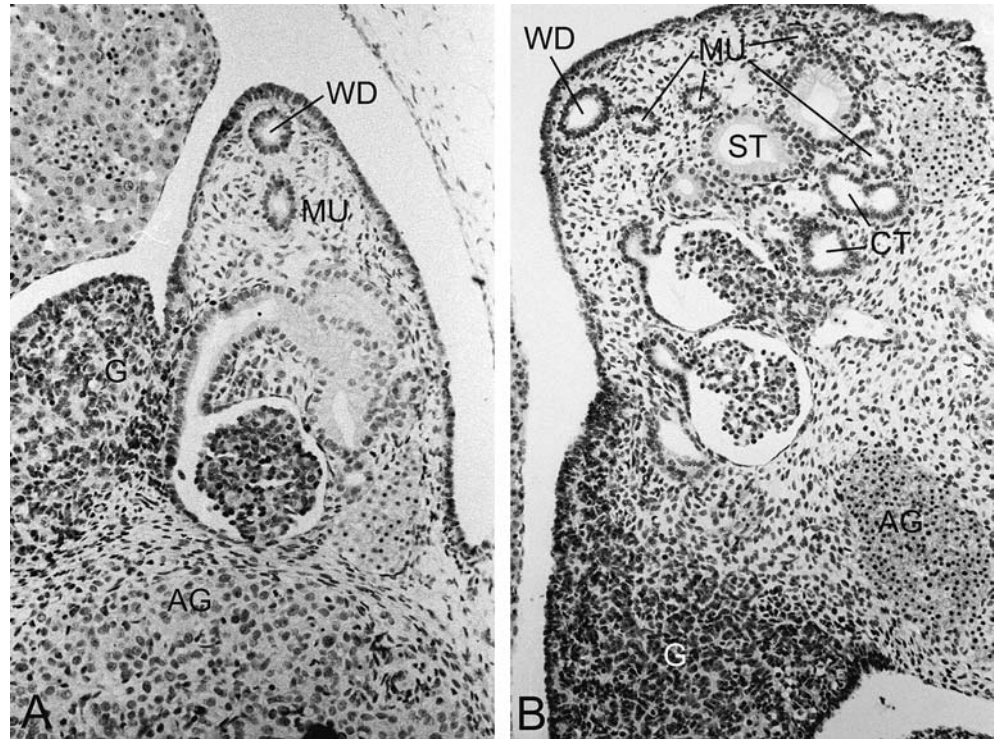
**Fig. 4** Embryo 17.5.51, 8 mm CRL (stage 15),  $\times 360$ . A whole nephron is exposed in this section. The secretory (proximal) tubule arising from the urinary pole of the corpuscle (\*) and bending sharply dorsally and medially becomes the collecting tubule at a distinct boundary (*arrowhead*). The latter, originally running close to the vascular pole of the corpuscle, but displaying no macula densa in this section, is bent sharply in dorso-lateral direction in order to join the mesoureter at a well defined site (*arrow*). Similar to the WD the mesoureter is characterized by cells with bright cytoplasm. Note orifice of the mesoureter in the mesonephric duct (+)



**Fig. 5** Embryo MJSp. 8.11.40, 15 mm CRL (stage 18).

**a** Section through the anlage of the epigenitale with the characteristic, densely arranged columnar cells belonging in part to the capsule of Bowman and in part to the initial portion of the secretory duct. They are apposed to the tissue of the gonad (*G*). Only a few tubules are visible due to their short length. On the lateral side, the *WD* and a mesoureter (*MU*) are situated in the urogenital fold. *AG* adrenal gland.  $\times 180$ .

**b** Section located 0.9 mm caudal from *A*. The fully functional paragenitale is separated from the gonad (*G*) by a thick layer of mesenchyma. All portions of the nephrons are visible. Note the mesoureters (*MU*) running up to the dorsal surface of the paragenitale (mesonephros). *ST* secretory tubule, *CT* collecting tubule, *AG* adrenal gland.  $\times 145$



bends sharply in the dorsal and medial direction. Its epithelium consists of faintly stained columnar cells with strongly stained granules in the apical cytoplasm. The subsequent tubulus collectivus shows a loop in the dorsal and lateral direction. Its origin is characterized by the macula densa; its epithelium is made up of densely arranged cuboidal cells with a homogenous and strongly stained cytoplasm. The collecting tubule leads in lateral direction to the section that has been generated by the conus of the mesonephric WD. In the literature, this part has been called in the “ureter of the mesonephros”; it is referred to as “mesoureter” in this paper. It is lined by the same epithelium as the WD, a cuboidal epithelium characterized by a clear, very faintly stained cytoplasm (Figs. 4, 5).

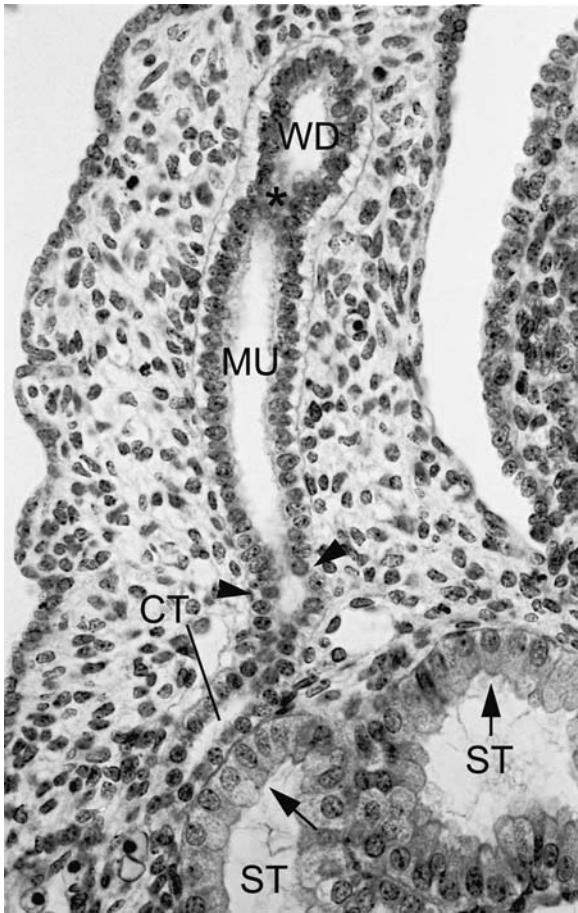
There are only 32–33 nephrons at stage 18 (13–17 mm CRL). The six most cranial nephrons are in the process of degeneration: they have no corpuscles, and their tubules consist of a homogenous epithelium. The caudal 26–27 nephrons are fully differentiated with glomeruli displaying epithelial plates and well differentiated tubular sections (Fig. 5). The 13–14 nephrons that will give rise to the epigenitale (Fig. 5a) can be well distinguished from the 13–14 nephrons that are going to form the paragenitale (Fig. 5b). In the prospective epigenitale, those parts of Bowman’s capsule and of the secretory tubule which are in contact with the hilus of the gonads, have been changed into a uniform, densely organized, columnar epithelium that is apposed like a beam to the hilus of the gonad (Fig. 5a). The paragenitale does not show such a transformation, and represents the secretory part of the mesonephros. Its corpuscles and secretory tubules are separated from the

gonad by loose mesenchyma (Fig. 5b). The mesoureters of the paragenitale have become longer; they can be followed up to the dorsal side of the tubular complex (Fig. 5b, cf Fig. 7) and be distinguished clearly from the collecting tubules by their epithelium which is characterized by the same bright cytoplasm as shown by the cells of the WD. Both epithelia are characterized by a very bright infranuclear area (Fig. 6). Only 26 intact nephrons are preserved by stage 20 (18–22 mm CRL) which are evenly distributed between epigenitale and paragenitale. The more cranial nephrons are atretic with completely missing corpuscles the tubular remnants consisting of a homogenous epithelium.

At the end of the embryonic period in stage 23 (27–31 mm CRL), the long drawn mesoureters form a peg-like structure situated laterally and slightly dorsally of the convolved tubules (Fig. 7): its back is formed by the WD, its teeth by the mesoureters. The histology of corpuscles and tubules gives the impression of a fully functional secretory organ. Out of a total of 33 nephrons the paragenitale contains 14 nephrons, the eight caudal of which have been reconstructed (Fig. 7). The central portion of the mesonephros consists of ten subsequent nephrons making up the epigenitale that in turn is followed by nine cranial nephrons almost completely degenerated.

## Discussion

The examination of the formation of nephrons (mesonephrons) and ureters (mesoureter) of the mesonephros yielded the following results summarized in Fig. 8. In



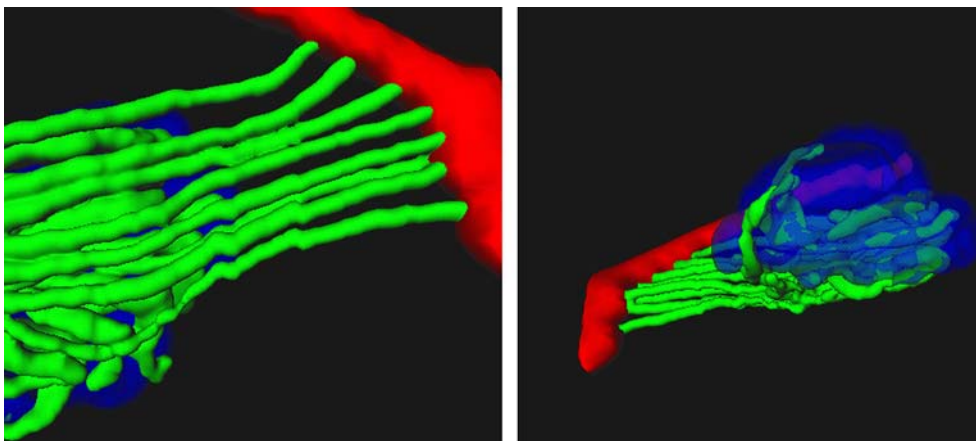
**Fig. 6** Embryo MJSp. 17.11.48, 20 mm CRL (stage 20),  $\times 360$ . The paragenitale of the mesonephros displays structures characteristic of full functionality. Secretory tubules (ST) with strongly stained columnar cells contain secreted material. Cells in between the secretory elements display microvilli (arrows). The collecting duct (CT) is clearly separated from the mesoureter (MU). Mesonephric duct (WD) and mesoureter (MU) have the same type of epithelium characterized by the bright subnuclear area. The orifice (\*) has been sectioned obliquely

stage 11 (2.5–4.5 mm CRL), a time point agreeing well with earlier reports (Torrey 1954), provascular cell masses are formed from the nephrogenic cord. This

process proceeds in cranio-caudal direction. As observed earlier (Ingalls 1907; Heuser 1930; Torrey 1954), the provascular cell masses differentiate into the mesonephros, which is in close contact with the mesonephric, WD. The contact point at the WD is characterized by palisade-like columnar cells (Fig. 8-1). Close to the basal lamina of the palisade, the cells of the provascular mass proliferate quickly, become columnar, and are arranged in a sickle-like shape (Fig. 8-2). The concavity of the sickle is filled by irregularly shaped, rounder cells, which in part are in contact with the WD and in part make a smooth transition into the surrounding tissue. A compact link with the WD is formed by further proliferation of these cells (Fig. 8-3), a structure that has been described as tubulus principalis (Heuser 1930; Torrey 1954). Its borderless continuity with the surrounding tissue has already been described by Meyer (1890). At the contact site, the WD generates a conically-shaped thickened epithelium (Fig. 8-3). Waldeyer (1870), who first observed this structure, proposed that the entire tubular system of a nephron is generated by these thickenings. Their presence is not uncontested: Meyer (1890) took these thickened areas in the wall of the WD as an artifact based on oblique sections, whereas Nagel (1889) confirmed them. They were not mentioned by Felix (1911) who, in addition, suggested that contact between WD and anlage of the nephron were only established by the growth of the vesicle.

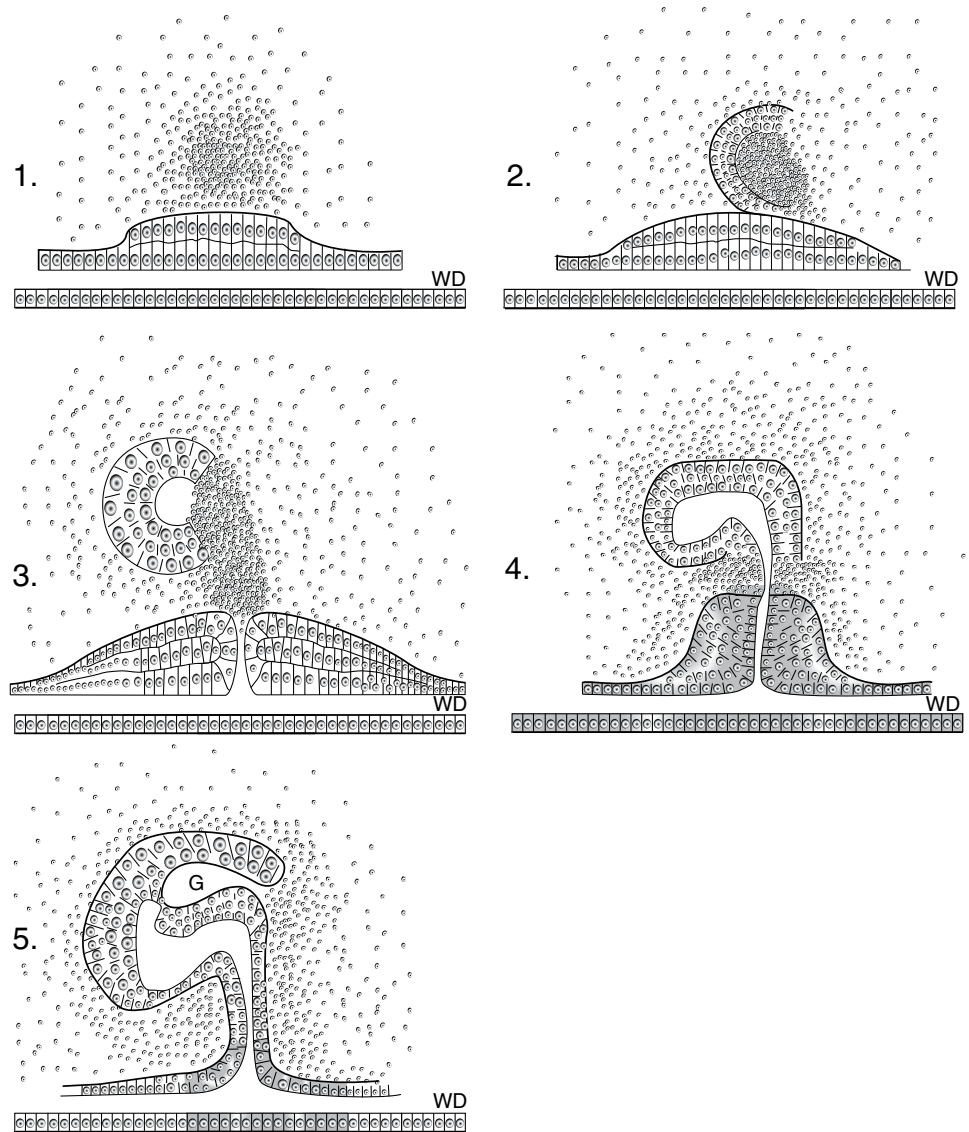
Formation of the lumen starts in stage 12 (3–5 mm CRL) and proceeds from cranial to caudal. The sickle-shaped structure is changed into a hollow sphere (the vesicle of the literature) with a wall consisting of a pseudostratified columnar epithelium. The lumen is

**Fig. 7** Embryo 10.12.52, 29 mm CRL (stage 23). Reconstruction of the eight caudal nephrons of the paragenitale of the mesonephros. The tubular lumen only is represented for clarity. The corpuscular surface is rendered in a transparent mode and false-colored blue. The lumen of the mesonephric WD is red, the mesoureters and the tubuli of the nephrons are green. The extended mesoureters run over the dorsal surface of the tubular and corpuscular complex towards the medial side. *Left*, dorsal view, slightly turned medially. *Right*, ventral view





**Fig. 8** Schematic representation of the consecutive steps involved in the development of the mesoureter from the Wolffian duct (WD) and the mesonephron. *G* pouch for the prospective glomerulus



generated by dehiscence of the cells. The sphere becomes separated from the WD and has now a basal lamina except at the site where it stays in contact with the conus of the WD by its compact stalk of irregular, rather spherical cells (Fig. 8-3, -4). Shortly after formation of the hollow sphere, dehiscence of cells generates a canaliculus in the compact stalk and conus of the WD (Fig. 8-4). The cells, which delineate the canaliculus by their apex, become columnar and form a pseudostratified epithelium with a newly formed, subjacent basal lamina (Fig. 8-4). By this process, the anlage of the nephron is finally delimited from the surrounding tissue. It now has a continuous lumen which flows into the canal of the WD conus, the anlage of the mesoureter (Fig. 8-5). The anlage of the nephron has gained by now the shape of a distillery flask with the hollow sphere as body of the flask and the stalk as outlet tube.

By stage 14 (5–7 mm CRL), the cell material of the nephrogenic cord is exhausted, thus preventing the formation of new nephrons. Counting yields a total of

36–40 newly formed nephrons, a number that agrees well with those referred in the literature (Kollmann 1898; Ingalls 1907; Shikunami 1926; Hayek 1969). Felix (1911) reports 32–39 nephrons in embryos of 7–13 mm CRL from which he deduces by arithmetics that are not completely transparent that 83 nephrons are formed in the human. This number, however, is found in amniotes, the definitive urinary organ of which is the mesonephros (for references see Felix 1903, 1906).

The formation of nephrons in the mesonephros such as those characterized above suggests that epithelio-mesenchymal interactions take place here that are very similar if not identical to those of the metanephros described by Saxén et al. (1986) and Dressler (2002).

In stage 15 (7–9 mm CRL) all mesonephrons display a characteristic S-bend and a ventral section that has become a corpuscle. On its lateral side is the urinary pole that gives rise to the secretory tubule, beginning with a sharp bend in the medial and dorsal direction. Its columnar cells are bright and contain darkly stained

granules in the apical cytoplasm. It is continued medially by the collecting duct, the epithelium of which is cuboidal and consists of intensely stained cells. The lack of transition between the two epithelia generates a sharp boundary between the tubular sections. More medially, the collecting tubule forms the macula densa at the site of contact with the corpuscle. This has been first described by Kozlik and Erben (1935), whereas DeMartino and Zamboni (1966) claim that there is no macula densa in the mesonephros. The second lap bends strongly to the dorsal and lateral side, and joins the mesoureter after a short distance. Due to the fact that cells of the mesoureter are very clear, the transition is apparent.

Up to stage 20 (18–22 mm CRL), the number of nephrons decreases. In stage 18 (13–17 mm CRL) 26–27 intact nephrons were present. The six most cranial no longer have a corpuscle. They are made up by an almost straight tubule that is delimited by a homogenous, cuboidal, strongly stained epithelium. The mesoureter has also been dedifferentiated. The epigenitale and paragenitale are formed from equal parts of the caudal 27 nephrons. The epigenitale is characterized by very high and strongly stained columnar cells in those parts of the corpuscle and secretory tubule that are apposed to the hilus of the gonad. This finding agrees with observations by Altschule (1930). The paragenitale is always separated from the hilus of the gonad by loose mesenchyma, a fact reported by Wilson (1926) and Altschule (1930). This part of the mesonephros represents its secretory portion and contains structures indicating functional ultrafiltration: Its glomeruli show epithelial plates (Silvermann 1969), which correspond to podocyte processes as shown by electron microscopy (DeMartino and Zamboni 1966).

The mesoureters behave differently in the two parts of the mesonephros. In the epigenitale they are short, straight and run medially to the junction with the tubule. In contrast, mesoureters of the paragenitale become long and even tubes running to the dorsal surface of the convolute of nephrons. At this location only do they interact with the collecting tubule. In stage 20 (18–22 mm CRL) there are still 26 nephrons. This number is confirmed by Felix (1911) and Hayek (1969). The cranial half among them belongs to the epigenitale, the caudal half makes up the paragenitale. More cranial nephrons are represented by short, twisted tubules without corpuscles. Thus, the so-called first period of dedifferentiation (Felix 1911), which designates degeneration of all mesonephrons not taken up by epigenitale and paragenitale, has been terminated (Wilson 1926). Its traces are vestigial tubules (hydatides) or a scar consisting of connective tissue (the cranial ligament of the mesonephros). Altschule (1930) relates a substantial number of degenerated nephrons without providing numbers. Shikunami (1926) illustrates a mesonephros of a stage 18 embryo displaying 26 intact mesonephrons caudal to 13 atretic ones. This is the largest number of mesonephrons in degeneration referred to in the literature. Felix (1911) claims that in the first period of dedifferentiation, 53

nephrons in total undergo degeneration which is an enigmatically high amount according to numbers found in this study and reported in the literature (see Hayek 1969).

In stage 23 (27–31 mm CRL) the paragenitale is still fully functional (Nagel 1889; Altschule 1930; O'Rahilly and Müller 1996). Felix (1911) and Fischel (1929) exclude an excretory function of the mesonephros and believe that the placenta takes over this function in the human.

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